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Prevention Conference VII
Obesity, a Worldwide Epidemic Related to Heart Disease and Stroke
Group III: Worldwide Comorbidities of Obesity

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Obesity is increasing in prevalence throughout the world (see the report by Group I), and with this change, there is a major increase in associated cardiac, metabolic, and other noncommunicable diseases.[1] This increase is particularly noticeable in countries in which there has not previously been an overweight and obesity problem, but it is also evident in countries in which obesity has been present for decades.

Although in the past, obesity had some positive societal implications, representing wealth, fertility, and power, in the later decades of the 20th century and now in the 21st century, the perception of overweight and obesity has changed in developed society and also has changed in most other societies. Obesity (the definitions of overweight and obesity are given in the 2000 World Health Organization [WHO] Technical Report[2] and elsewhere in this report) now is seen as a social hindrance and is known to be associated with disease. Visceral or intraabdominal obesity, in contrast to subcutaneous or lower-body obesity, carries the greatest risk of cardiac and metabolic diseases. However, we must still recognize that overweight and obesity are part of a continuum and that health risks increase with increasing weight in the individual.

Associated Diseases and Disorders

Mortality

The mortality associated with excess weight increases as the degree of obesity and overweight increases. One study estimated that between 280 000 and 325 000 deaths annually in the United States could be attributed to obesity.[3] More than 80% of these deaths occur among people with a body mass index (BMI) >30 kg/m^2. The increase in death from obesity has been documented in a number of studies from around the world (Table 1).

In the Nurses' Health Study,[4] the risk of death in women with a BMI >19 kg/m^2 rose progressively. Mortality was lowest among women who weighed at least 15% less than the US average for women of similar age and among those whose weight had been stable since early adulthood. The American Cancer Society's Prevention Study I has shown that among 62 116 white men and 262 019 white women (both groups were healthy nonsmokers and were followed up for 14 years), a greater BMI was associated with increased death rate from all causes and from cardiovascular disease in both groups up to age 75. The impact of the excess body weight was higher among younger subjects than it was among older ones.[5] In an even larger study (457 785 men and 588 369 women) with a 14-year follow-up (American Cancer Society's Prevention Study II), the association of BMI and mortality was affected by smoking status and history of other disease. Among the nonsmokers, the lowest mortality for men was in the BMI group 23.5 to 24.9 kg/m^2 and for women it was in the BMI group 22.0 to 23.4 kg/m^2. Among subjects with a BMI >40 kg/m^2, the relative risk of death was 2.6 times higher for men and 2.0 times higher for women compared with those who had a BMI between 23.5 and 24.9 kg/m^2. Black men and women had lower risks than corresponding categories of whites. No effect of age existed, and the risk of death or cardiovascular disease did not significantly increase over the BMI range 22.0 to 26.4 kg/m^2 for men and 20.5 to 24.9 kg/m^2 for women.[6] In the Aerobics Center Longitudinal Study, 25 714 men were observed for up to 10 years. The all-cause and cardiovascular mortalities were higher in men with a

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TABLE 1. All-Cause and Disease-Specific Cause of Death From Several Epidemiological Studies in Relation to Body Mass Index

	All-Cause Mortality*	
Study and BMI Criteria, kg/m^2	Male	Female
Nurses Health Study[9] (age 30–55 y, with 16 years' follow-up)		
19.0–21.9	...	2.46
22.0–24.9	...	2.46
25.0–26.9	...	2.61
27–28.9		3.35
29–31.9	...	3.90
>32	...	4.64
British Regional Heart Study[10] (age 40–59 y, with 13.8 years' follow-up)		
20–21.9	12.6	...
22–23.9	11.5	...
24–25.9	11.8	...
26–27.9	11.8	...
28–29.9	13.3	...
>30	16.8	...
Gothenberg Birth Cohort[11] (age 47–55 y, with 19.7 years' follow-up)		
20.0–22.5	15.5	...
22.5–25.0	13.9	...
25.0–27.5	14.3	...
27.5–30	16.6	...
>30	21.1	...
Cancer Prevention Study II (age 65–74 y)[6]		
22.0–23.4	8.54	4.98
23.5–24.9	8.98	5.95
25.0–26.4	9.41	5.98
26.5–27.9	10.38	6.36
28.0–29.9	12.70	7.96
30.0–31.9	13.70	8.36
32.0–34.9	17.98	11.11
>35.0	27.67	12.99

*Deaths/1000 patient-years.

BMI >30 kg/m^2 and lowest in men with a BMI 18.5 to 24.9 kg/m^2. Men with a BMI of 25 to 29.9 kg/m^2 had a mortality falling in between.[7] The deaths from cardiovascular disease increased from a little more than 5 deaths/10 000 man-years with a body fat of <16.7% to nearly 8 deaths/10 000 man-years in men with a body fat of 16.7% to 25.0% and to nearly 12 deaths/10 000 man-years in men with a body fat >25.0%. The association between obesity and the risk of death from coronary heart disease (CHD) was confirmed by a study of 8373 Finnish women (aged 30 to 59 years) observed for 15 years.[8] This study found that for each increase of ≈1 kg in body weight, the risk of coronary mortality increased by 1% to 1.5%. A substantial part of this risk was mediated through the link between body weight and blood pressure.

Cardiovascular Disease

Foremost in the global burden of cardiovascular diseases are CHD and stroke. The Global Burden of Disease Study ranked these conditions first and second among all categories of death in worldwide mortality for 1990.[12] The same study projected that by 2020 these conditions would persist in the first and second ranks among causes of death. They also were predicted to hold first and fourth ranks in terms of disability-adjusted years of life lost (an index that takes into account age at death and years of disability for survivors with these conditions). Closely related clinically but not separately analyzed is heart failure due to atherosclerosis and hypertension. Heart failure doubtless adds considerably to the burden of cardiovascular diseases throughout the world. However, estimation of this component of heart disease is not reliable because of even more limited data and is further complicated by the major contributions of other conditions, such as rheumatic heart disease, Chagas disease, and cardiomyopathies, to the burden of heart failure in many countries.[13]

The World Heart Federation has compiled extensive data on the burden of cardiovascular diseases in major geopolitical regions of the world (information available at www.world-heart.org).[14] By 1996, the proportion of deaths attributable to circulatory conditions already was estimated to be 29.0% worldwide, 45.6% in developed countries, and 24.5% in developing countries; the latter increased from 16%—or by one half—as estimated by the WHO in 1980.[15] The corresponding increases from 1990 to 2010 in the industrial market economies, economies in transition, and developing countries were projected to be 1.8%, 19.4%, and 28.2%, respectively.[14] Thus, the global burden of these cardiovascular conditions is great and growing.

Variation among countries in the occurrence of these conditions was first investigated systematically in the Seven Countries Study, beginning in the late 1950s and 1960s.[16] A >10-fold range in incidence of CHD was found in the Seven Countries Study among 16 cohorts of middle-aged men in Europe, Japan, and the United States. These differences were explained primarily by differences in dietary fat consumption, blood cholesterol concentration, and blood pressure among the cohorts and not by differences in BMI. This finding was possibly the result of the narrow range and mainly "normal" mean values of BMI at baseline among the cohorts.[17] In addition, because of the prior wartime dietary conditions of most of these populations at the time of baseline examinations, the BMI may have measured relatively more lean mass and less fat mass than would be the case for today's populations in the same areas.

A similarly wide range of incidence and mortality rates from CHD was shown in the WHO MONICA Project, conducted from the mid-1980s through mid-1990s in 31 countries.[18] The majority of study populations were from Europe, although populations from Australia, China, New Zealand, and the United States were included. Ten-year trends in fatal and nonfatal CHD events were compared with trends in BMI as measured in population samples in the same study areas. The results depended on inclusion or exclusion of anomalous findings from 5 populations in the Commonwealth of Independent States that experienced a decline in

BMI. Only after exclusion of these populations from analysis did change in BMI contribute importantly to the observed trends in coronary event rates, explaining 31% and 10% for men and women, respectively, of the observed variation in trends in event rates.

On a population-wide basis, the contribution of the continuously graded distribution of BMI to the pandemic occurrence of CHD and stroke appears to have two essential aspects. First is the relation of BMI to mortality independent of the major risk factors, including blood cholesterol concentration, blood pressure, and smoking. Second is the more immediate relation of BMI to the risk factors themselves. These two aspects are illustrated by data from Finland, based on a 15-year follow-up of more than 13 000 men and women aged 30 to 59 at examination in 1972 or 1977 in North Karelia.[8] Throughout the distribution of baseline values of BMI, CHD death rates increased for men; for women, rates increased from <18.5 kg/m^2 to 20 to 31.9 kg/m^2 and increased further for those at or >32 kg/m^2.

The regression coefficients for BMI and CHD mortality for both men and women were evaluated by adjustment for major risk factors (eg, smoking, total cholesterol concentration, systolic blood pressure) separately and together. The results indicated that the BMI–coronary mortality relationship was influenced by all three factors. Consistent with extensive data from other sources, BMI was associated directly with both blood lipids and blood pressure and inversely with smoking. In addition, significant relationships between BMI and coronary mortality persisted after this adjustment for both men and women. Subjects with diabetes at baseline for this study were excluded; however, new-onset diabetes may have had an influence on risk estimates.[8] Overall, BMI appears to contribute to the development of other major risk factors (eg, blood lipids, blood pressure) and independently to CHD mortality.

As the prevalence of overweight has increased in pediatric age groups, so has the frequency of diagnosis of the complications of obesity that typically have been seen in the adult population. Risk factors for the development of coronary artery disease coexist in obese adolescents.[19] Hyperlipidemia, hyperinsulinemia, and early atherosclerosis are seen more commonly among obese adolescents than they are in normal weight cohorts. In the Bogalusa Heart Study nearly 60% of obese children had 1 risk factor for cardiovascular disease and 20% had 2 or more risk factors.[20]

Although only limited data are available to estimate the contribution of obesity, as measured by BMI or other indices, to the risk of stroke, the role of obesity in the development of blood lipids and blood pressure argues for an important contribution to the risk of stroke, especially hemorrhagic stroke.[13]

The following conclusions can be stated about cardiovascular disease:

- Atherosclerotic and hypertensive cardiovascular disorders, especially CHD and stroke, are pandemic in their global occurrence, which is projected to increase dramatically in the next 2 decades, and constitute the leading cause of death and disability in the world population.

TABLE 2. Estimates of Regional Prevalence of Diabetes in 2000 and 2010 in Millions of Cases

Region	2000	2010	Increase, %
North America	14.2	17.5	23
Europe	26.5	32.0	24
Australia	1.0	1.3	33
South America	15.6	22.5	44
Africa	9.4	14.1	50
Asia	84.5	132.3	57
World average	151	221	46

Data from Zimmet et al, 2001.[21]

- The underlying risk factors are equally widespread and reflect demographic, economic, and social changes that result from local, national, regional, and global influences on multiple sectors of society.
- The prevalence of obesity, defined as a BMI of ≥ 30 kg/m^2, is increasing rapidly in many populations throughout the world, among both children and adults, with varying rates of increase in specific groups. Underlying this phenomenon is a longstanding, widespread shift in the population distribution of BMI, as documented for the United States in birth cohorts from the late 19th to the late 20th centuries.[15]
- The contribution of obesity to risk of cardiovascular diseases, partly through the development of other major risk factors and partly through direct effects on CHD and possibly on stroke, is a major reason for concern about the rising frequency of obesity.
- Obesity and its consequences are in principle preventable. In this era of its high and growing prevalence, the prevention of obesity is a necessary component of strategies to prevent not only heart disease and stroke but their major risk factors as well.

Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is strongly associated with obesity in all ethnic groups. More than 80% of cases of T2DM can be attributed to obesity, which also may account for many diabetes-related deaths. Projections by the WHO show an alarming rate of increase in the prevalence of diabetes over the next decade. As can be easily seen in Table 2, important regional differences are found in the rate of increase. At the low end are North America, Europe, and Australia. Asia is the area with the greatest growth rate, making it the area in which preventive strategies are the most important.

The risk of T2DM increases with the degree and duration of obesity and with central distribution of body fat. A study of 51 000 male health professionals in the United States[22] found a strong positive association between overall obesity (measured by BMI) and the risk of diabetes. The relative risk for diabetes in men with a BMI of 35 kg/m^2 was 40 times higher than that for men with a BMI of 23 kg/m^2. A similarly strong curvilinear relationship between BMI and the risk of T2DM was found in women.[23] The lowest risk was associated with a BMI <22 kg/m^2, and at a BMI >35 kg/m^2 the relative risk for diabetes adjusted for age increased to 61 kg/m^2. The risk

may be further increased by a sedentary lifestyle or decreased by exercise. Weight gain after age 18 in women and after age 20 in men also increases the risk of T2DM. Weight gain precedes the onset of diabetes. Among Pima Indians (a group with a particularly high incidence of T2DM), for example, body weight gradually increased 30 kg (from 60 kg to 90 kg) in the years preceding the diagnosis of diabetes.[24] After the diagnosis of diabetes, a small decrease in body weight occurred. In long-term follow-up studies there was also a strong relationship between the duration of obesity and the change in plasma glucose concentrations during an oral glucose tolerance test.

Conversely, weight loss is associated with a decreased risk of T2DM. In the Swedish Obesity Study diabetes was present in 13% to 16% of obese subjects at baseline.[25] Among those who underwent gastric bypass and subsequently lost weight, 69% with diabetes were cured, and only 0.5% of those who did not have diabetes at baseline developed the disorder. In comparison, obese subjects who did not lose weight had a higher incidence of T2DM (7.8%). Individuals with impaired glucose tolerance participating in the Diabetes Prevention Program (DPP) involving a lifestyle modification program, which included 150 min/wk of exercise and a weight loss of 7% body weight, had a 58% reduction in the progression to diabetes.[26] The risk reduction associated with the lifestyle intervention in the DPP study was the same as that in a smaller trial conducted in Finland,[27] and was higher than the reductions associated with diet (31%), exercise (46%), and diet plus exercise (42%) in a study in China.[28]

Insulin Resistance

Insulin resistance with hyperinsulinemia is characteristic of obesity and is present before the onset of hyperglycemia. With obesity early demonstrable changes are alterations of insulin-mediated antilipolysis, impairment in glucose removal, and increased insulin resistance, which result in hyperinsulinemia. This hyperinsulinemia is associated with increases of hepatic very-low-density triglyceride synthesis (VLDL triglyceride), plasminogen activator inhibitor-1 synthesis, sympathetic nervous system activity, and sodium reabsorption. These changes contribute to dyslipidemia and hypertension in subjects who are obese. The insulin resistance characteristic of T2DM probably results from a combination of obesity and genetic factors. In a study of nondiabetic offspring of two parents with T2DM insulin sensitivity was similar to that of normal subjects (with no first-degree relatives with T2DM and at near ideal body weight). With increasing degrees of obesity a progressive decrease in insulin sensitivity was much more pronounced in those with a family history of T2DM.[29] The mechanism by which obesity induces insulin resistance is poorly understood. Many factors may be important and interactive, including free fatty acids (FFA), tumor necrosis factor-alpha (TNF-α), the pattern of fat distribution, and multiple genetic abnormalities.

Liver Disease

Nonalcoholic fatty liver disease (NAFLD) has become recognized as one of the most common abnormalities observed in obese individuals. NAFLD refers to a wide spectrum of liver disease. Classically, suspicion of NAFLD is raised by an elevation of serum transaminases in the absence of excessive alcohol intake, negative serology for viral hepatitis, no autoimmune disease, and the lack of other known causes of liver disease. Imaging studies are consistent with steatosis. When performed, the liver biopsy shows steatosis, inflammatory cell infiltration with portal predominance often surrounding ballooned hepatocytes, and fibrosis that will eventually progress to severe cirrhosis. Nonalcoholic steatohepatitis (NASH), a term used in earlier reports of liver disease associated with obesity, represents only one stage within the spectrum of NAFLD.[30–32] It is not clear why simple steatosis develops only in some individuals, whereas others progress to severe cirrhosis. It has been estimated that severe fibrosis occurs in up to 50% of obese individuals and cirrhosis develops in 7% to 16%.[33–35] Dyslipidemia and insulin resistance both are strongly associated with the presence of NAFLD, and limited data suggests that a correlation may exist between the severity of the metabolic disorder and the severity of liver disease.[30]

Analysis of the National Health and Nutrition Examination Survey III (data collected from 1988 to 1994) used criteria for NAFLD diagnosis of the presence of 1 or more elevated liver enzyme value with no alternative explanation. The prevalence of NAFLD increased with increasing BMI and increased with increasing waist circumference, and men had a greater likelihood of NAFLD than women at all ages.[30] Overall, NAFLD has been reported to affect 10% to 24% of populations of various countries and up to 74% of obese individuals.[31]

Weight loss often has showed improvement in the underlying liver disease, although with rapid weight loss there have been observations of worsening of the histological findings.[31] The most effective rate of weight loss awaits further study. No documented pharmacological treatment has been shown to be effective, although good medical management of glucose levels and lipid levels should be encouraged.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a disease associated with obesity that is characterized by loud snoring and repetitive closure (apnea) or partial closure (hypopnea) of the upper airway during sleep. The increasing respiratory efforts to overcome airway closure lead to arousals from sleep and fragmentation of normal sleep patterns. The major daytime complaint is excessive daytime sleepiness (EDS) that results from disturbed sleep. About 25% of middle-aged men and 9% of middle-aged women have OSA[36,37] (defined categorically as an apnea-hypopnea index [AHI] >5). OSA with significant EDS occurs in about 2% and 4% of middle-aged women and men, respectively.[37]

Actual apneic events are associated with increased blood pressure, cardiac arrhythmia, and increased muscle sympathetic nerve activity.[38] When awake, patients with OSA have increased muscle sympathetic nerve activity, even adjusting for the effects of obesity.[38] Evidence is increasing that OSA is a risk factor for the development of hypertension, ischemic heart disease, congestive heart failure, stroke, and consequently, premature death.[38,39] Even patients with mild degrees of OSA are at a much greater risk of developing hypertension

than those without after adjusting for all major known risk factors.[40] Moreover, a very high prevalence of OSA in drug-resistant hypertension has been observed.[38] Insulin resistance also is associated with OSA independent of obesity.[41] More recent studies show that OSA is associated with higher levels of various atherogenic mediators. Treatment of OSA can reduce the levels of these mediators. There is also recent randomized clinical trial data showing that blood pressure is reduced by medium-term treatment of OSA with nasal continuous positive airway pressure.[42]

All epidemiological investigations have shown consistently that obesity, especially central obesity, is strongly associated with OSA[36,37,43] Conversely, OSA is overrepresented in obese subjects.[43] It has been suggested that a considerable part of the excess morbidity in the obese population is mediated by OSA.[43] Weight loss can reduce OSA severity,[44] but controlled or long-term data are limited.

Musculoskeletal Disorders

The incidence of osteoarthritis is increased in obese subjects and accounts for a major component of the cost of obesity.[45] Osteoarthritis commonly develops in the knees and ankles; this may be directly related to the trauma associated with excess body weight. It also occurs more frequently in non-weight-bearing joints, suggesting that components of the obesity syndrome alter cartilage and bone metabolism independent of weight bearing. In one study of more than 1000 women, obesity was classified as the upper tertile of BMI; the middle tertile had a BMI range of 23.4 to 26.4 kg/m^2. The age-adjusted odds ratios of unilateral and bilateral osteoarthritis at the knee, determined from x-ray films of the knees comparing the high and low tertiles of BMI, were 6.2 and 18, respectively.[46] Lesser increases occurred in the odds ratio for arthritis in various joints, between the middle and lower tertiles. A twin study found similar results; each kilogram increase in body weight (compared with a twin control) was associated with an increased risk of radiographic features of osteoarthritis at the knee and carpometacarpal joint.[47] Weight loss is associated with a decreased risk of osteoarthritis. In a study of 800 women a decrease in BMI of $\geq$2 kg/m^2 in the preceding 10 years decreased the odds for developing osteoarthritis by more than 50%.[48] This benefit also was found among those women with a high risk for osteoarthritis due to a high baseline BMI ($>$25 kg/m^2). Chest pain produced by mechanical problems in the back because of obesity also is common.

Cancer

A working group of the International Agency for Research on Cancer (IARC) of the WHO reviewed the association between overweight and cancer and concluded that sufficient evidence exists for a cancer-preventive effect of avoidance of weight gain (prevention of overweight).[49] This evidence has been obtained for cancers of the colon, breast (in postmenopausal women), endometrium, kidney (renal cell), and esophagus (adenocarcinoma). For premenopausal breast cancer the available evidence on the avoidance of weight gain suggests the lack of a cancer-preventive effect.

Fertility

Both infertility and hirsutism are more common in obese than in nonobese women. In part this is due to the capacity of adipose tissue to aromatize androgens to estrogens or metabolize them to other androgens. Despite this fact, obesity usually is not associated with alterations in plasma gonadotrophin (eg, luteinizing hormone, follicle-stimulating hormone) levels or the hypothalamic-pituitary control of these hormones. Polycystic ovarian syndrome and moderate obesity are frequently associated, and many of the women with this condition have insulin resistance[50] and/or other components of the metabolic syndrome. Many women enrolled in in vitro or assisted fertilization programs are overweight or obese. A small weight loss will increase both fertility and success of the program.

Other Disorders

Obesity is associated with a wide range of comorbidities and these were well covered in the WHO Technical Report.[2] Additional metabolic problems include hyperuricemia and gout, and a direct relationship exists between obesity and gallbladder disease, which increases with age. Varicose veins are common because of increased pressure, and lymphoedema may result. Skin ulcerations and deep venous thrombosis are common in persons with grade III obesity (BMI $>$40). Pulmonary embolism may occur,[2] particularly in persons with decreased mobility. Cor pulmonale, sometimes associated with sleep apnea, also can occur.

In addition to these medical factors, a great many psychosocial problems are associated with obesity. Obese people have a reduced quality of life, are more likely to be divorced (men) or never married (women), to have fewer employment prospects, and to be stigmatized socially.[51–56]

Modifying Factors

Fat Distribution and the Metabolic Syndrome

BMI is most widely used as an indicator of overall fatness. Variation in BMI may reflect variation in lean body mass and fat mass but not the distribution of fat. The waist circumference tends to reflect both total and regional fatness, especially in the higher age ranges.[57] It is commonly accepted that accumulation of fat in the abdominal region is particularly related to an increased risk of cardiovascular disease through its association with the metabolic syndrome. Individuals with the metabolic syndrome are at increased risk for developing diabetes mellitus and cardiovascular disease.[58] Abdominal obesity, as measured by a large waist circumference, is part of the National Cholesterol Education Program Adult Treatment Panel III definition of the metabolic syndrome. Patients having 3 or more of the following criteria are defined as having the metabolic syndrome:

1. Abdominal obesity: waist circumference $>$102 cm in men and $>$88 cm in women.
2. Hypertriglyceridemia: $\geq$1.69 mmol/L
3. Low high-density lipoprotein cholesterol: $<$1.04 mmol/L in men and $<$1.29 mmol/L in women
4. High blood pressure: $\geq$130/85 mm Hg
5. High fasting glucose: $\geq$6.1 mmol/L

Metabolic syndrome is prevalent in the United States.[59] The age-adjusted prevalence was found to be about 24% in US adults and increased sharply with age.

Waist circumference is closely linked to the amount of intraabdominal or visceral adipose tissue. The main hypothesis linking visceral adipose tissue accumulation to the metabolic syndrome, T2DM, and cardiovascular disease is through hepatic overexposure to fatty acids.[60] Visceral fat is characterized by high lipolytic activity and by drainage by the portal vein. Alternative or additional explanations exist for a relationship between fat mass and the metabolic syndrome. First, adipose tissue is an endocrine organ secreting many peptides that have been linked to aspects of the metabolic syndrome.[61] These peptides include leptin, resistin, adiponectin, angioteninogen, interleukin-6, TNF-α, adipsin, and plasminogen activator inhibitor-1.[55] Some of these proteins are inflammatory cytokines, some play a role in lipid metabolism, and others are involved in vascular hemostasis or the complement system. Second, several hormonal factors may be underlying factors that are related to both abdominal fat distribution and dyslipidemia and insulin resistance. Examples are high androgen levels in women (low levels in men), increased concentrations of glucocorticoid hormones, low levels of growth hormone and insulin-like growth factor-1.[62] It has been established that in mice the overexpression of 11-β hydroxysteroid dehydrogenase type 1 in adipose tissue leads to increased visceral adipose tissue, hypertension, and insulin resistance.[63] Behavioral factors such as sedentary lifestyle, smoking, and dietary habits may be related to the increased accumulation of abdominal fat as well as other components of the metabolic syndrome.[62]

Thus, although the exact mechanisms underlying the associations remain to be fully elucidated, an increased accumulation of abdominal fat, as reflected by an increased waist circumference, is an important diagnostic tool in addition to BMI.

Some investigators have suggested the use of other ratios (eg, waist-to-hip, waist-to-thigh, sagittal abdominal diameter–to–thigh). The rational for using these ratios is that the numerator reflects a combination of total and abdominal fat mass and the denominator reflects overall body size or regional body tissue mass (peripheral fat or muscle) that must be accounted for. Because measurement errors may be compounded in a ratio and because the interpretation of these ratios in pathophysiological terms in difficult, the public health applications of these ratios might be limited. Simple measurements (eg, waist circumference) are more likely to be useful in public health efforts.[57]

Age/Aging

The development of the comorbidities of obesity, particularly those related to cardiovascular disease, strongly interact with aging and in fact are predominantly middle-age in onset. Changing body composition, with increasing proportion of fat with aging, may underlie the associations among obesity, aging, and many of these cardiovascular comorbidities. With the increase of obesity at younger ages, features of these comorbidities are beginning earlier. Adipose tissue is now recognized as an endocrine organ, and many of the hormones and cytokines it produces are under intense investigation for their possible roles as mediators of comorbidities.

Researchers in aging have long recognized that energy restriction is the single most powerful intervention to slow aging processes, reduce the diseases associated with aging, and extend life span. First demonstrated in rodents, the extraordinary power of energy restriction to mitigate and/or prevent the diseases associated with aging has been shown to be true in nonhuman primates.[64,65] These effects appear to depend on the reduction and maintenance of reduced body fatness. The converse appears to be happening in humans (the removal of energy restraints that previously played preventive roles) based on much epidemiological data across ethnic, cultural, and regional groups, and this plays a significant role in the development of obesity and cardiovascular diseases. Experimental interventions also have demonstrated that energy restriction reduces dyslipidemia in primates,[65] prevents T2DM,[64] and slows other diseases of aging, including hypertension and some cancers.[66] Thus evidence is mounting that with energy restraint to prevent obesity or to reduce excess adiposity, the comorbidities of obesity also will be in large measure prevented.

Region/Ethnicity

Evidence is accumulating that different ethnic groups may be affected differently or at different BMIs than others. For example, in Japanese populations, the relative risk of hypertension is 3 at a BMI of 24.9 kg/m^2, with the nadir of risk at a BMI of 22.6. In Chinese populations evidence exists that diabetes risk starts at a much lower BMI and doubles within the defined "healthy" range of BMI; the same is true of the Australian aboriginal population.[67] These and other lines of evidence have led to the suggestion that in Asian populations the BMI ranges for "action points" may need to be revised, with a BMI of 25 kg/m^2 indicating the need for treatment.[68] In Japan a BMI of 25 kg/m^2 is accepted as obesity grade I. The Working Group on Obesity in China, after a review of 13 data sets containing 240 000 people and 4 cohort studies with 70 000 subjects, have suggested that a BMI of 24 kg/m^2 may represent overweight in China and obesity is a BMI $>$28 kg/m^2. Obviously differences exist in both the type of comorbidity and the BMI at which it occurs in Asian and other populations. It has been suggested that the occurrence of comorbidities at lower BMIs may be the result of greater adiposity in Asians, in particular visceral adiposity.[68,69] Conversely, it has been suggested that Pacific Island populations may be protected, having greater lean body mass at any BMI.[70,71] These problems need to be studied further.

Gender

The prevalence of obesity is higher in women in most ethnic groups and is reflected in differences in comorbidities. The risk of developing diabetes, hypertension, gallbladder disease, and coronary artery disease differs by ethnic group and by gender within ethnic group. This is particularly evident for those with BMI $>$40 kg/m^2 but also is present at BMIs between 30 and 40 kg/m^2. In white women the risk of T2DM is greater than the risk of hypertension, which in turn is greater than the risk of gallbladder disease. Although the risk of diabetes also is high in white men, the risk of gallbladder

disease exceeded that of hypertension. In African American and Mexican American men the risk of hypertension was higher than that of diabetes. In African American women the risks of diabetes and gallbladder disease were higher, whereas in Mexican American women risks of CHD, diabetes, and gallbladder disease were similar, and the odds ratio was less than in corresponding African American or white women. These ethnic and gender differences undoubtedly reflect the interaction of genetic and environmental factors.

Research Directions

Obesity is increasing in prevalence throughout the world. Obesity is a "risk factor" for cardiovascular disease, and with its increasing prevalence there are increases in metabolic disease (particularly T2DM) and many other disorders and these have been detailed in this chapter.

Important areas for research and intervention include the following:

1. Long-term longitudinal studies to determine whether the risks of obesity for cardiovascular disease and metabolic disease, in particular, are the same across all populations and ethnic groups; these studies will help answer whether specific (or lower) action points in specific populations are needed or whether different approaches for the prevention of cardiovascular and metabolic diseases are needed
2. Studies to determine the specific factors that determine weight (adipose tissue) gain and particularly those factors that predispose individuals to abdominal adiposity
3. The development of effective weight maintenance programs and studies to determine whether they will reduce cardiovascular (and other disease) morbidity and mortality
4. The development of strategies for the prevention of obesity, which may be directed at children and adolescents, at-risk populations, or the population as a whole; these studies and interventions need to be applied regionally, assessed rigorously, and those which are effective applied generally (few effective population strategies exist, and it must be expected that not all strategies will be successful)
5. Prevention of obesity in childhood and adolescence expected to contribute to the prevention of dyslipidemia and hypertension; studies at the clinical and then the population level are needed to evaluate the effectiveness of interventions against obesity on these further endpoints
6. Studies to determine whether the effectiveness of weight-loss interventions is greater than the benefits of controlling comorbidities through medical management
7. Studies to increase our knowledge of control of fat cell deposition and its relationship to disease risk
8. Studies to identify the determinants of why certain individuals do not develop overweight or obesity
9. Studies to help translate improved knowledge into actual lifestyle modification (behavior change)
10. Studies to assess the relative benefits of weight loss versus increased physical activity

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KEY WORDS: AHA Scientific Statements ■ obesity ■ cardiovascular diseases ■ exercise ■ diet